NOTIFICATION.

(LAW DEPARTMENT).

No LAW 117 LOR 62, dated Bangalore, 9th August 1962

Ordered that the accompanying Notification No. G S R. 984, dated the 12th July 1962, of the Ministry of Health, amending the Drugs Rules, 1945, which has been published in the *Gazette of India*, Part II, Section 3, sub-section (i), dated the 21st July 1962, be republished in the *Mysore Gazette*, for general information.

By Order and in the name of the Governor of Mysore,

S SRIPADARAJ,
Under Secy. to Govt, L. D.

GOVERNMENT OF INDIA.

MINISTRY OF HEALTH.

New Delhi, the 12th July 1962.

G S R. 984 —In exercise of the powers conferred by sub-section (*d*) of Section 6 and Sections 12 and 33 of the Drugs Act, 1940 (23 of 1940), the Central Government after consultation with the Drugs Technical Advisory Board, hereby makes the following rules further to amend the Drugs Rules, 1945, the same having been previously published as required by the said Sections 12 and 33, namely —

1 These rules may be called the Drugs (First Amendment) Rules, 1962.

2 In the Drugs Rules, 1945 (hereinafter referred to as the said rule), in rule 44 for clause (b), the following clause shall be substituted, namely —

"(*b*) has a first or second class degree in Pharmaceutical Chemistry or Pharmacy, or a post-graduate degree in Chemistry with Pharmaceutics as a

special subject from a University recognised for the purpose by the appointing authority or the Associateship Diploma of the Institution of Chemists (India) obtained by passing the examination with "Analysis of Drugs and Pharmaceuticals" as one of the subjects and has had not less than two years' post-graduate experience in the analysis of drugs in a laboratory under control of (i) a Government Analyst appointed under the Act, or (ii) a Chemical Examiner to Government, or (iii) a Fellow of the Royal Institute of Chemistry of Great Britain (Branch E), or (iv) the head of an institution specially approved for the purpose by the appointing authority; or

3. In rule 46 of the said rules (*b*) for the words "protocols of the tests applied" the word "protocols of the tests or analysis applied" shall be substituted,

(*b*) the following Explanation shall be added at the end, namely:—

"*Explanation*.—It shall be deemed to be full and sufficient compliance with the requirement of the rule in respect of the supply of "protocols of the tests or analysis applied," If—

(1) for pharmacopoeial drug, where the tests or methods of analysis prescribed in the official pharmacopoeia are followed, references to the specific tests or analysis in the pharmacopoeias are given in the report;

(2) for patent or proprietary medicines for which the tests and methods prescribed in any of the official pharmacopoeias are applicable and are followed, references to the specific tests or analysis in the pharmacopoeias are given in the report,

(3) for patent or proprietary medicines containing pharmacopeial drugs for which the official tests or analysis or methods of assays are modified and applied, a description of the actual tests or, as

the case may be, analysis or methods of assays so applied is given in the report,

(4) for patent or proprietary medicines for which no pharmacopœial tests or methods of analysis are available or can be applied but for which tests or methods of analysis given in standard books or journals are followed, a description of such tests or methods of analysis applied together with the reference to the relevant books or journals from which the tests or methods of analysis have been adopted, is given in the report,

(5) for those drugs for which methods of test are not available and have been evolved by the Government Analyst, a description of tests applied is given in the report."

4. In rule 49 of the said rule for clause (a), the following clause shall be substituted, namely —

"(a) has a degree in Pharmacy or Pharmaceutical Chemistry or a post graduate degree in chemistry with pharmaceutics as a special subject of a University recognised for this purpose by the appointing authority or the Associateship Diploma of the Institution of Chemists (India) obtained by passing the examination with "Analysis of Drugs and Pharmaceuticals" as one of the subjects, or"

5. For sub-rule (5) of rule 69, of the said rule, the following sub-rule shall be substituted, namely —

(5) "Applications by licensees to manufacture additional items of drugs shall, in the case of a licence to manufacture for sale and distribution other than repacking, be made to the Licensing Authority Such applications shall, if the additional items of drugs applied for belong to categories not already included in the licence, be accompanied by a fee of rupees ten for each additional category of drugs specified in Schedule M."

6. In Form 13 of said rule in paragraph 7, for the word "protocols of test" the following shall be substituted, namely —

"protocols of test or analysis".

7 In Form 24 of the said rule, for paragraph 2, the following paragraph shall be substituted, namely —

"2 Names of drugs categorized according to Schedule M"

8 In Form 25, of the said rules, (1) in paragraph 1, for clause (b), the following clause shall be substituted, namely —

"(b) Names of drug (each item to be separately specified) "

or "condition 3", the following conditions shall be substituted, namely —

"3 If the licensee wants to manufacture for sale additional items of drugs not included above he should apply to the Licensing Authority for the necessary endorsement as provided in rule 69(5). This licence will be deemed to extend to the categories so endorsed."

9. In Schedule F, of the said rule for Part VIII, the ollowing Part shall be substituted, namely —

"PART VIII—ADRENALINE INJECTION".

1. Proper Name.—The proper name of the preparation shall be "Adrenaline Injection".

2. Description.—Adrenaline Injection is a sterile solution of adrenaline in water for injection containing in each 1,000 ml 0 08 g tartaric acid, 0 8 g Sodium Chloride and not less than 0 09 g. and not more than 0 110 g of Adrenaline, C_9H_1 303N.

3 Standard Preparation.—The standard preparation is a quantity of pure l-Adrenaline which complies with the following tests —

Test of identity and purity.—(1) It gradually darkens on exposure to air It combines with acids, forming salts which are soluble in water, and from these solution, the base may be precipitated by the addition of dilute solution of ammonia or by alkali carbonates.

(2) It is very slightly soluble in water and in dehydrated alcohol, more soluble in boiling water, practically insoluble in alcohol (90 per cent), in ether, in chloroform, in acetone, and in fixed and volatile oils.

(3) It is not stable in a neutral or alkaline solution which rapidly becomes red on exposure to air.

(4) Dilute 1 ml. or 0 1 per cent w/v solution in water with 4 ml of water and add 1 drop of a 10 0 per cent w/v solution of ferric chloride in water, an emerald green colour is immediately produced which becomes cherryred on the addition of 4 drops of solution of dilute ammonia (Indian Pharmacopoeia)

(5) Add 1 ml of 0·1 per cent w/v solution in water to 5 ml of a 10 0 per cent w/v solution of sodium acetate in water, and add 2 drops of test solution of mercuric chloride (Indian pharmacopoeia). A red colouration slowly appears which reaches its greatest depth of intensity after half an hour When the tube is placed for not more than 10 to 15 seconds in boiling water—both the colour appears more quickly.

Specific rotation —Determined at 25°C in a 4 0 per cent w/v solution in a mixture of 1 volume of hydrochloric acid and 9 volume of water,—50 0° to 53·5°

Adrelanone —0·05 g, dissolved completely in a mixture of 0 15 ml of water and 0 15 ml of acetic acid

Loss on drying —When dried to constant weight at 100° in vacuo loses not more than 1·0 per cent of its weight

Residue on Ignition.—Not more than 0 1 per cent.

4. Test for Potency —A suitable solution of adrenaline injected intravenously into a cat or a dog by the methods below produces a rise in the systolic bloodpressure of the animal corresponding to that produced by an equal amount of a solution of standard chemically pure adrenaline.

Preparation of the solution for the test —The following method is suggested.—

Weight accurately about 0 050 g. of standard adrenaline dissolved it in 5 ml of N/I Hydrochloric acid and dilute this to 50 ml by the addition of distilled water, thus making a I in 1,000 solution must be recently prepared, otherwise it deteriorates. It will keep for a short time if preserved in hard glass containers in a refrigerator, but it must be discarded if any signs of deterioration, such as colouration, are observed.

Suitable dilutions of the standard adrenaline solution may then be made in physiological saline for comparison with equivalent dilutions of adrenaline injection to be tested.

Methods of comparison of potency —The following methods of assay are suggested —

(*a*) For the purpose of the assay a full grown cat, preferably male, should be used The cat should be anaesthetised with a suitable anaesthetic, the spinal cord should be divided and the brain destroyed, the respiration being maintained artificially. The blood pressure is estimated by inserting a cannula into the carotid artery and connecting the same with a mercury manometer which records on a moving drum. The injections are made into the exposed femoral vein. The blood-pressure must be low and must not vary before experiments are started. The amount of standard solution necessary to cause a submaximal rise in blood pressure by injecting intravenously varying doses of the solution at regular intervals should be determined and after

a satisfactory dose has been ascertained the uniformity of reactions should be tested by the injection of two or more doses of equal size. If these injections produce approximately equal increases in blood-pressure alternate injections of the solution to be tested and of the standard are made varying amount of the unknown until two or more successive injections raise the blood-pressure to the same height, indicating that the amount of active agent is the same in the doses used From the result thus obtained the strength of the unknown solutions may be determined and adjusted.

(*b*) For the purpose of the assay, a dog of medium size should be used The animal should be anaesthetised with a suitable anaesthetic and maintained under artificial respiration. It is prepared for blood pressure estimations by inserting a cannula into the carotid artery and connecting the same with a mercury manometer which records on a moving drum. The injections are made into the exposed femoral vein Before the test is made, if in case any muscular movement such as twitching is present, the dog should receive by intravenous injections a sufficient dose of curare, but if the animal is deeply anaesthetised, this is not necessary. The dog should also receive a sufficient dose of atropine sulphate (from 0 ·01 g to 0 002 g per kg of the dog's weight) to paralyse the vagi, this paralysis being proved by electrical stimulation. Injections must be made at regular intervals of approximately five minutes.

Determine the amount of standard solution necessary to cause a rise in blood-pressure from 30 to 60 mm of mercury by injecting intravenously varying dose of the solution and after a satisfactory dose has been ascertained, the uniformity of reaction should be tested by the injection of two or more doses of equal size If these injections produce

approximately equal increases in blood-pressure, alternate injections of the solution to be tested and of the standard are made varying the amount of the unknown until two or more successive injections raise the blood pressure to the same height indicating that the amount of active agent is the same in the doses used From the results thus obtained the strength of the unknown solution may be determined and adjusted

5. Containers —(1) Ampoules shall be made of resistant glass that passes the tests for limits of alkalinity of glass as laid down in the Indian Pharmacopoeia. Containers other than ampoules shall be made of amber coloured resistant glass that passes the test for limit of alkalinity of glass as laid down in the Indian Pharmacopoeia.

(2) The drug shall be made up only in single-dose containers of 0 5 ml or 1 ml capacity.

(3) The anti-oxidant or preservative which may be added to the solution need not be specified in the formula

6. Storage —Adrenaline Injection shall be kept in ampoules protected from light If the solution becomes brown in color or contains a precipitate, it must be rejected A suitable preservative, may be added to the solution.

Labelling —The label of the container shall contain the following in addition to any other particulars prescribed in these rules —

1. Strength of the solution.
2 The word 'Sterile'.
3. Dose (0-12 to 0-5 ml by injection)
4 Date of manufacture and date of expiry, the intervening period must not exceed twelve months.
5 The name and strength of any preservative or antioxidant added shall be shown either on the label of the container or on the package in which the container is enclosed for sale.

7 Caution —If solution is brown in colour or contains a precipitate it must be rejected."

19. For Schedule M, of the said rules, the following Schedule shall be substituted, namely —

"SCHEDULE M"

(*See* rules 71, 71-A and 76)

(1) *Requirements of Factory premises*

(A) Location and surroundings — The factory shall be situated in a place which shall not be adjacent to an open sewage, drain, public lavatory or any factory which produces a disagreeable or obnoxious odour or fumes or large quantites of soot, dust or smoke. The factory shall be located in a sanitary place, remote from filthy surroundings

(B) Buildings —The buildings used for the factory shall be constructed so as to permit of production under hygienic conditions They shall conform to the conditions laid down in the Factory Act, 1948 (63 of 1948). The part of the building used for manufacture shall not be used as a sleeping place and no sleeping place adjoining to it shall communicate therewith except through open air or through an intervening open space

The walls of the room in which manufacturing operations are carried out shall, up to a height of six feet from the floor, be smooth, water-proof and must be capable of being kept clean The flooring shall be smooth, even and washable and shall be such as not to permit of retention or accumulation of dust. There shall be no chinks or crevices in the walls or floor.

(C) Water supply —The water used in manufacture shall be pure and of drinkable quality, free from pathogenic micro-organisms

(D) Disposal of waste —Waste water and other residues from the laboratory which might be prejudicial to the workers or to public health shall be disposed of after suitable treatment to render them harmless.

(E) Health, Clothing and Sanitary requirement of the Staff —All workers shall be free from contagious or obnoxious disease Their clothing shall consist of a white or coloured uniform suitable to the nature of work and the climate, and shall be clean. Adequate facilities for personal cleanliness, such as clean towels, soap and handscrubbing brushes shall be provided separately for each sex. The workers shall be required to wash and change into clean footwear before entering the rooms where the manufacturing operations are carried on. The workers shall also be required to wear either a clean cap or a suitable head gear so as to avoid any possibility of contamination by hair or perspiration. For those engaged in filling and sealing of containers for parenternal preparations, suitable cotton masks should be provided to cover the nostrills and mouth during work.

(F) Medical services —The manufacturer shall provide ,

(1) Adequate facilities for First Aid.

(2) Medical inspection of workers at the time of employment and periodical check up thereafter at least once a year.

(3) Facilities for vaccination and inoculation against the enteric or any other epidemic group of diseases.

Adequate precautions for safeguarding the health of the workers, including measures to avoid industrial accidents or diseases.

(G) Working benches shall be provided for carrying out operations such as filling, labelling, packing etc Such benches shall be fitted with smooth, impervious tops capable of being washed.

(H) In factories where operations involving the use of containers, such as, bottles, vials, jars, ampoules, are conducted, there shall be adequate arrangements separated from the manufacturing operations for washing, cleansing and drying such containers with suitable equipment for the purpose. Sterilising facilities where necessary should also be provided.

(2) Requirements of Plant and Equipment

(*A*) *The following equipment is recommended for the manufacture of Ointments, Emulsion or Lotions and Suspensions*

1 Mixing tanks
2. Kettle, steam, gas or electrically heated
3 A suitable power-driven mixer
4 Storage tanks or pots
5 A colloid mill or a suitable emulsifier
6. A triple roller mill or an ointment mill
7 Liquid filling equipment
8 Jar or tube filling equipment

An area of 300 square feet is recommended for the basic installations

(B) *The following equipment is recommended for manufacture of Syrups, Elixirs and Solutions* —

1 Mixing and storage tanks
2 Portable mixer.
3. Filter press or other suitable filtering equipment, such as metafilter or sparklet filter.
4. Vacuum or gravity filler
5 Water still or Deioniser

An area of 300 square feet is recommended for the basic installations

(*C*) *Equipment for the manufacture of Pills and Compressed Tablets including Hypodermic Tablets.*—For efficient operation the tablet production department shall be divided into three distinct and separate Sections —

(*a*) Granulating Section
(*b*) Tabletting Section
(*c*) Coating Section

The following equipment is recommended in each of the three Sections.

(*a*) *Granulating Section* —

1 Disintegrator
2 Powder Mixer
3 Mass Mixer
4. Granulator
5. Ovens, thermostatically controlled,

(*b*) *Tabletting Se tion* —

1 Tablet machine, single punch or rotary
2. Pill machine
3 Punch and dies storages cabinet.
4 Tablet counter

The Tabletting Section shall be free from dust and floating particles For this purpose, it is desirable that each tablet machine is connected either to an exhaust system or isolated into cubicles

(*c*) *Coating Section* —

1 Jacketed kettle, steam, gas or electrically heated, for preparing solution
2 Coating pan
3 Polishing pan
4 Heater and exhaust system

The coating section shall be made dust-free and suitable exhaust provided to remove excess powder and the fumes resulting from solvent evaporation. An area of 300 square feet for each of the above three Sections is recommended for basic installations.

The manufacture of Hypodermic Tablets shall be conducted under aseptic conditions in a separate air-conditioned room the walls of which shall be smooth and washable The granulations, tabletting and packing shall be done in this room

(*D*) *The following equipment is recommended for the manufacture of Powders*

1 Distintegrator
2. Mixer
3 Sifter
4 Stainless steel vessels and scoops of suitable material.
5 Filling equipment

In case of operations involving floating particles of fine powder or dust a suitable exhaust system shall be provided. Workers should be provided with suitable mask during operation.

An area of 300 square feet is recommended to allow for the basic operation Where the actual powdering is to be done on the premises an additional room shall be provided for the purpose

(*E*) *The following equipment is recommended for filling of Hard in Gelatin Capsules*

1 Mixing and blending equipment
2 Capsule filing units.
3 Capsule counters

An area of 200 square feet is recommended for the basic installations for capsules filling The room shall be air-conditioned and also dehumidified wherever necessary.

In case of operations involving floating particles of fine powder of dust a suitable exhaust system shall be provided.

(F) *The following equipment is recommended for the manufacture of Surgical Dressings other than Absorbent Cotton Wool*

1 Rolling machine
2 Trimming machine
3. Cutting equipment
4 Folding and pressing machine for gause
5 Mixing tanks for processing medicated dressings
6 Hot air drying ovens
7 Steam steriliser or dry heat steriliser.

An area of 3^0 square feet is recommended to allow for the basic installations In case medicated dressings are to be manufactured, another room with an area of 3(0 square feet shall be provided.

(*G*) *The following equipment is recommended for manufacture under aseptic conditions of Eye-Ointments Eye-drops, Eye-Lotions and other Preparations for external use*

1. Hot air oven electrically heated with thermostatic control
2 Kettle, gas or electrically heated with suitable mixing arrangement
3 Colloid mill or ointment mill.

4. Tube filling equipment
5 Mixing and storage tanks of stainless steel or of other suitable material
6 Sintered glass funnel, Seitz filter or filter candle.
7 Liquid filling equipment.
8. Autoclaves.

An area of 250 square feet is recommended for the basic installations. The manufacture and filling shall be carried out in an air-conditioned room under aseptic conditions. The room shall be further behumidified if preparations containing anti-biotics are manufactured

(*H*) *The following equipment is recommended for manufacture of Pessaries and Suppositories*

1. Mixing and pouring equipment.
2. Moulding equipment

An area of 200 square feet is recommended to allow for the basic installations

In case of pessaries manufactured by granulation and compression, if the licensee does not have a tablet section, a separate area of 500 square feet and the following equipment is considered necessary

1. Mixer
2. Granulator.
3. Drier.
4. Compressing machine
5. Pessary and Tablet counter.

(*I*) *The following equipment is recommended for manufacture of Inhalers and Vitrallae*

1. Mixing eqipment.
2 Graduated delivery equipment for measurement of the medicament.
3. Sealing equipment

An area of 200 square feet is recommended for the basic installations

(*J*) *The following equipment is recommended for the repacking installations of drugs and Pharmaceutical chemicals*

1 Sifters.
2 Stainless steel scoops and vessels.
3 Weighing and measuring equipment
4 Filling equipment

An area of 300 square feet is recommended for basic packing operations In case of operations involving floating particles of fine powder or dust a suitable exhaust system should be provided.

(*K*) *Requirements for the manufacture of Parenteral Preparations*

The whole process of the manufacture of parenteral preparations may be divided into the following seperate operations

(*a*) *Preparations of the container.*—This includes, cutting, washing, drying and sterilisation of ampoules or vials prior to filling.

(*b*) *Preparations of solution* —This includes preparations and filtration of solution.

(*c*) *Filling and sealing* —This includes filling and sealing of Ampoulesor filling and capping of vials

(*d*) Sterlisation.

(*e*) Testing

The following basic hygienic requirements shall be complied with

(1) Strict sanitation shall be maintained throughout the entire plans in order to prevent contamination and to keep out pyrogens. Masks and overalls shall be worn wherever necessary.

(2) The preparation room where the solutions are prepared shall be tiled and kept scrupulously clean This room shall be air-conditioned

(3) The filling and sealing rooms shall likewise be air-conditioned under positive pressure with air locks provided to prevent the entry of air from out side The walls and floors shall be tiled so as to permit their being sprayed and washed with an antiseptic solution The benched shall preferably have stainless steel or laminates plastic tops capable of being washed

(4) In the room provided for aseptic filling and sealing, a sufficient number of sterilising lamps shall be mounted over the benches and in the air lock leading to the room to prevent contamination

(5) A separate room shall be provided for sterilisation testing (for leaks and floating particles) and drying

(6) Separate arrangements for labelling and packing

(7) Finished products shall be stored in a separate cool and dry area.

The following equipment is recommended

Manufacturing Area

1. Storage equipment for ampoules and vials
2 Ampoule washing and drying equipment
3 Dust proof storage cabinets
4 Water Still
5. Mixing and preparation tanks or other containers

The tanks or containers shall be made of either glass or such material as will not react with the liquid

6. Filtering equipment such as filter press or sintered glass funnel
7. Autoclave
8 Hot Air Steriliser

Filling and sealing room

9 Benches for filling and sealing
10 Filling and sealing unit
11 Aseptic filling and sealing room
12 Bacteriological filters such as Seitz filter, filter candles or sintered glass filters.
12 Filling and sealing unit.

General Room

13 Inspection table
14 Leak testing equipment
15 Labelling and packing benches
16 Storage equipment including cold storage and refrigerators, if necessary.

An area of 600 square feet partitioned into suitably sized cubicals, is recommended for the basic installations.

NOTE —The above requirements of Schedule M are subject to modifications at the discretion of the licensing authority if he is of the opinion that having regard to the nature and extent of the manufacturing operations it is necessary to relax or alter them in the circumstances of a particular case "

[No F 1-60/61-D]

A C RAY, Under Secy.